December 5, 2002

Walter L. Jones
Pine Chemicals Association, Inc
1117 Perimeter Center West
Suite 500E
Atlanta, Georgia 30338

Dear Mr. Jones:

The Office of Pollution Prevention and Toxics is transmitting EPA's comments on the robust summaries and test plan for the Rosin Esters Category, posted on the ChemRTK HPV Challenge Program Web site on January 18, 2002. I commend The Pine Chemicals Association for its commitment to the HPV Challenge Program.

EPA reviews test plans and robust summaries to determine whether the reported data and test plans will provide the data necessary to adequately characterize each SIDS endpoint. On its Challenge Web site, EPA has provided guidance for determining the adequacy of data and preparing test plans used to prioritize chemicals for further work.

EPA will post this letter and the enclosed Comments on the HPV Challenge Web site within the next few days. As noted in the comments, we ask that the Pine Chemicals Association advise the Agency, within 90 days of this posting on the Web site, of any modifications to its submission.

If you have any questions about this response, please contact Richard Hefter, Chief of the HPV Chemicals Branch, at 202-564-7649. Submit questions about the HPV Challenge Program through the "Contact Us" link on the HPV Challenge Program Web site pages or through the TSCA Assistance Information Service (TSCA Hotline) at (202) 554-1404. The TSCA Hotline can also be reached by e-mail at tsca-hotline@epa.gov.

I thank you for your submission and look forward to your continued participation in the HPV Challenge Program.

Sincerely,

-S-

Oscar Hernandez, Director
Risk Assessment Division

Enclosure

cc: C. Auer
A. Abramson
W. Penberthy
M. E. Weber

EPA Comments on Chemical RTK HPV Challenge Submission:
Rosin Esters Category

SUMMARY OF EPA COMMENTS

The sponsor, The Pine Chemicals Association, Inc., submitted a test plan and robust summaries to EPA for the Rosin Esters Category dated January 18, 2002. EPA posted the submission on the ChemRTK HPV Challenge Web site on February 26, 2002. The category consists of seven members.

EPA has reviewed this submission and has reached the following conclusions:

1. Category Justification. The submitter's support for grouping the chemicals under this category is adequate.

2. Physicochemical Properties and Environmental Fate. The submitter needs to provide melting point, boiling point, vapor pressure, and transport and distribution (fugacity) data for the compounds in this category. The submitter also needs to provide photodegradation data for two chemicals in the category.

3. Health Effects. (a) EPA disagrees that an acute toxicity study on rosin pentaerythritol ester is necessary given other available data (acute and repeated-dose toxicity). (b) EPA agrees with the submitter's proposal to conduct additional testing for two representative members of the category, rosin pentaerythritol ester and partially hydrogenated rosin methyl ester, to address reproduction/developmental toxicity endpoints. However, EPA recommends that rosin methyl ester be tested instead of partially hydrogenated rosin methyl ester (see discussion under Test Substance) for a combined repeated-dose/reproduction/developmental toxicity screening test. (c) Further testing is also necessary for both genotoxicity endpoints for the category because the negative cancer study is not sufficient to address these endpoints.

4. Ecological Effects. EPA does not agree with the submitter's proposal to conduct acute aquatic testing for two representative members of the category. EPA recommends only one chronic 21-day invertebrate test be conducted on rosin methyl ester due to the low water solubility and estimated log $K_{ow} < 7.5$. EPA believes other category members will not show aquatic acute or chronic effects based on their physicochemical properties.

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.

EPA COMMENTS ON THE ROSIN ESTERS CATEGORY
CHALLENGE SUBMISSION

Category Definition

The rosin esters category consists of the following seven members:

Name	CAS No.
Rosin, pentaerythritol ester	8050-26-8
Rosin, glycerol ester	8050-31-5
Rosin, diethylene glycol ester	68153-38-8
Rosin, methyl ester	68186-14-1
Rosin, hydrogenated, glycerol ester	65997-13-9
Rosin, hydrogenated, pentaerythritol ester	64365-17-9
Rosin, partially hydrogenated, methyl ester	8050-15-5

The first four chemicals are unsaturated rosin esters, and the remaining three members are saturated rosin esters. All members of the category are derived from pine tree rosin and are complex mixtures; for example, the commercial products produced from pentaerythritol are mixtures of primarily tetra- and triesters with some di- and monoesters.

The category definition is clear and unambiguous.

Category Justification

The submitter's basis for this category is that these substances are all esters of rosin that follow a pattern of increasing molecular weight and whose physicochemical, environmental fate, and toxicological properties will likely relate to that pattern. EPA agrees with this category approach.

Test Substance

The submitter has selected rosin pentaerythritol ester and partially hydrogenated rosin methyl ester as the two representative substances of this category for the ecotoxicity and reproductive/developmental tests. The submitter states that these two substances represent the extremes of the properties of the members of this category. Rosin pentaerythritol ester has one of the highest molecular weights in the category and has the highest softening point. Partially hydrogenated rosin methyl ester has one of the lowest molecular weights in the category and has the lowest softening point. EPA agrees with this approach for selecting test substances, but recommends rosin methyl ester (an unsaturated ester) be tested instead of partially hydrogenated rosin methyl ester for health effects testing because, unlike the saturated methyl ester, the unsaturated ester may undergo epoxidation during metabolism and thereby be more toxicologically active.

Test Plan

Physicochemical Properties (melting point, boiling point, vapor pressure, water solubility, and partition coefficient).

The submitter's proposal to test for partition coefficient and water solubility is adequate for the purposes of the HPV Challenge Program.

Melting Point. The submitter states in the test plan that no testing is required for the melting point and that

"melting points values cannot be determined because the compounds in this category are mixtures and either will not give a sharp melting point when heated or will decompose before they melt." The submitter, however, provided softening points for some of the substances which satisfy the testing requirement. EPA agrees with the submitter's reasoning since the softening points adequately reflect the entire category. However, the submitter should identify which mixtures decompose upon heating and which mixtures have a broad softening point. These softening points should be provided in the robust summaries.

Boiling Point. The submitter states that the boiling point values cannot be determined for chemicals in this category because "these substances are complex mixtures and will undergo oxidation or partial decomposition before they boil." However, OECD Guideline 103 states that "measurements at reduced pressure may be appropriate for substances with a high boiling point and substances which decompose at elevated temperatures." The submitter should provide a technical discussion as to why measuring the boiling point at reduced pressure is not appropriate for this category of compounds. The submitter should also discuss the oxidation and partial decomposition of chemicals in this category. Supportive information, such as thermal or calorimetric analysis (which might illustrate partial decomposition) as described in OECD Guideline 103 would be useful to illustrate the submitter's conclusions. EPA recommends that the boiling point for CAS No. 68153-38-8 should be measured as no data have been provided and it is a good representative substance.

Vapor Pressure. The submitter states in the test plan that testing is not required for vapor pressure since the vapor pressures for these substances at ambient temperatures are effectively zero. The submitter provides no evidence to support this conclusion. OECD Guideline 104 states that a calculated value for vapor pressure may be acceptable if it is less than 10^{-5} Pa ($7.5x10^{-5}$ mm Hg). Using EPIWIN, EPA obtained estimated values of 6.65×10^{-5} mm Hg for CAS No. 68186-14-1, and 1.44×10^{-5} mm Hg for CAS No. 8050-15-5, which are near the threshold value. All the other substances in this category have estimated vapor pressure values less than the threshold. The submitter needs to provide measured vapor pressure data for CAS No. 68186-14-1, and 8050-15-5; and estimated data for all the other substances in the category.

<u>Environmental Fate (photodegradation, stability in water, biodegradation, fugacity)</u>.

EPA agrees with the submitter's approach for stability in water and biodegradation. The submitter needs to follow OECD Guideline 301 for the biodegradation testing.

Photodegradation. The submitter states that because all of the category members have negligible vapor pressure, no testing is necessary for this endpoint. However, CAS No. 68186-14-1, and 8050-15-5 have estimated vapor pressures greater than 10^{-6} mm Hg at 25°C, which suggest that they will partially exist in the vapor phase. For these chemicals, atmospheric oxidation may be important; therefore, the submitter needs to provide atmospheric oxidation estimates.

Fugacity. The submitter states that "due to the inability to provide usable inputs to the required model, no determination of transportation and distribution between environmental compartments will be undertaken for rosin esters." EPA disagrees. By using structurally analogous compounds that represent the chemical mixtures for each of the 7 classes, the fugacity calculations are possible. Available measured values should be used as inputs into the fugacity model to estimate the environmental distribution of the representative compounds. When estimating transport and distribution, EPA recommends that the submitter use the level III model rather than the level I and II models because it provides a more sophisticated level of analysis.

<u>Health Effects (acute toxicity, repeated-dose toxicity, genetic toxicity, and reproductive/developmental toxicity)</u>.

Adequate data are available for acute toxicity on CAS No. 68186-14-1 and 8050-15-5 and for repeated-dose toxicity on CAS No. 8050-26-8, 8050-31-5, 65997-13-9, and 64365-17-9. EPA does not agree that an acute toxicity test is necessary on CAS No. 8050-26-8 given the available acute and repeated-dose toxicity data (90-day and carcinogenicity studies). EPA agrees with the submitter's proposal to conduct additional testing for two representative members of the category, CAS No. 8050-26-8 and 8050-15-5, for reproduction/developmental toxicity endpoints. However, EPA recommends that CAS No. 68186-14-1 be tested instead of CAS No. 8050-15-5 (see discussion under Test Substance) for a combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422), to address these health endpoints for the category for the purposes of the HPV Challenge Program.

Acute Toxicity. The submitter categorized the acute oral toxicity data for CAS No. 8050-31-5 as adequate in Table 1, but provided no robust summaries in support of this categorization. The compound would be more appropriately labeled "C" (category read-down) because no data have been provided for this category member.

Genetic Toxicity. EPA disagrees with the submitter's statement that the negative carcinogenicity study on CAS No. 8050-26-8 satisfies the genotoxicity endpoints. The study failed to meet a number of the parameters in OECD TG 453, including group size and, most importantly, multiple exposure concentrations. No systemic effects, such as "depressed weight gain at the highest dose" as described in the test plan, were seen at the single dose reported in the robust summary. Apparently the maximally tolerated dose was not achieved, and the study is inadequate to support the submitter's contention that the testing requirement for rosin pentaerythritol ester is met. In addition, the genetic toxicity endpoint is distinct from carcinogenicity and cannot be satisfied by carcinogenicity data alone, because mutations are implicated in several other disease state. Examples include Down's and Klinefelter syndromes, cystic fibrosis, hemophilia, sickle-cell anemia, achondroplastic dwarfism, hypercholesterolemia, hypertension, pyloric stenosis, glaucoma, allergies, and mental retardation (Mutagenicity Risk Assessment Guidelines, EPA 1986).

Three different robust summaries were submitted for genotoxicity tests for CAS No. 8050-31-5, each indicating negative results. However, these studies were inadequate since none of the studies tested concentrations up to the limits of toxicity or solubility, and the highest dose tested did not meet the requirements of a limit test.

Therefore, EPA believes that the genotoxicity endpoints (gene mutations and chromosomal aberrations) are not adequately addressed in the discussion of the test plan and recommends that the submitter conduct additional testing on CAS No. 8050-26-8 and 68186-14-1.

Table 1 on page 5 should be corrected to show gene mutation and chromosomal aberration, rather than bacterial and non-bacterial assays, as the two endpoints for genotoxicity.

Reproductive Toxicity. The submitter needs to recategorize the reproductive toxicity data for CAS No. 8050-26-8, 8050-31-5, 65997-13-9, and 64365-17-9 in Table 1. EPA believes that this endpoint has not been adequately addressed for any of these category members for the purposes of the HPV Challenge Program because only repeated-dose toxicity studies are available with no existing adequate developmental toxicity data; therefore, EPA recommends that a combined repeated-dose/reproduction/developmental toxicity screening test (OECD TG 422) be performed on CAS No. 8050-26-8. These compounds would be more appropriately labeled "test" for CAS No. 8050-26-8 or "C" for CAS No. 8050-31-5, 65997-13-9, and 64365-17-9.

<u>Ecological Effects (fish, invertebrates, and algae)</u>.

EPA disagrees with the submitter's proposal to perform acute testing for all ecotoxicity endpoints (fish, daphina and algae) of two representative substances to address these endpoints for the category because chronic toxicity is likely to occur with these substances. EPA recommends only one chronic 21-day invertebrate test be conducted on CAS No. 68186-14-1 due to the low water solubility and estimated log K_{ow} < 7.5. EPA believes other category members will not show aquatic acute or chronic effects based on their physicochemical properties. Because the calculated log K_{ow} for CAS No. 68186-14-1 is lower than that for CAS No. 8050-15-5, it is more amenable to aquatic test conditions and is the preferred test substance. EPA agrees with the submitter's approach to conduct the study "under conditions that maximize the solubility under the specific test exposure conditions, but reduce exposure to insoluble fractions" (page 19 of the Test Plan) and to investigate the effects of changes in pH. As to the effect of filtration on toxicological responses, EPA believes that filtration is unnecessary for this chemical and should be avoided if possible. More information on testing difficult chemicals such as poorly water-soluble substances can be found in the Guidance Document on Aquatic Toxicity Testing of Difficult Substances and Mixtures (OECD, June 2000), available at http://www.oecd.org/ehs/test/monos.htm.

Specific Comments on the Robust Summaries

Health Effects.

Acute Toxicity. Missing information for the robust summaries of CAS No. 68186-14-1 includes: insufficient animals per group (1-3/dose for rats, 1-6/dose for guinea pigs, 1-3/dose for rabbits), insufficient study observation period (10 days), and lack of body weight or clinical observation data in all species.

Followup Activity

EPA requests that the submitter advise the Agency within 90 days of any modifications to its submission.